

INDOLE-TYPE DERIVATIVES AS INHIBITORS OF p38 KINASE

This application is a CIP of SN 09/316,761 filed 05/21/1999 now US Pat. No. 6,589,964;
which is a CIP of SN 09/275,176 filed 03/24/1999 now US Pat. No. 6,340,685;
which is a CIP of SN 09/128,137 filed 08/03/1998 now US Pat. No. 6,130,235;
which claims priority benefit of 60/086,531 05/22/1998,
5 which claims priority benefit of 60/154,594 09/17/1999,
which claims priority benefit of 60/202,608 05/09/2000.

Field of the Invention

The invention relates to treating various disorders associated with enhanced
activity of kinase p38- α . More specifically, it concerns compounds that are related to
10 indole-type derivatives coupled to piperazine- or piperidine-type moieties as useful in
these methods.

Background Art

A large number of chronic and acute conditions have been recognized to be
associated with perturbation of the inflammatory response. A large number of cytokines
15 participate in this response, including IL-1, IL-6, IL-8 and TNF. It appears that the
activity of these cytokines in the regulation of inflammation rely at least in part on the
activation of an enzyme on the cell signaling pathway, a member of the MAP kinase
family generally known as p38 and alternatively known as CSBP and RK. This kinase is
activated by dual phosphorylation after stimulation by physiochemical stress, treatment
20 with lipopolysaccharides or with proinflammatory cytokines such as IL-1 and TNF.
Therefore, inhibitors of the kinase activity of p38 are useful anti-inflammatory agents.

Eye diseases associated with a fibroproliferative condition include retinal
reattachment surgery accompanying proliferative vitreoretinopathy, cataract extraction
with intraocular lens implantation, and post glaucoma drainage surgery.

25 PCT applications WO98/06715, WO98/07425, and WO 96/40143, all of which
are incorporated herein by reference, describe the relationship of p38 kinase inhibitors
with various disease states. As mentioned in these applications, inhibitors of p38 kinase
are useful in treating a variety of diseases associated with chronic inflammation. These